



# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY REC'D 24 NOV 2005

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>A160073</b>	<b>FOR FURTHER ACTION</b>  See Form PCT/PEA/416	
International application No. <b>PCT/IB2004/002527</b>	International filing date (day/month/year) <b>27.07.2004</b>	Priority date (day/month/year) <b>08.08.2003</b>
International Patent Classification (IPC) or national classification and IPC <b>C07D281/16</b>		
Applicant <b>VITA CIENTIFICA, S.L. et al. [Signature] (9233)</b>		
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p style="margin-left: 20px;">a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau) a total of 2 sheets, as follows:</p> <p style="margin-left: 40px;"><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p style="margin-left: 40px;"><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p style="margin-left: 20px;">b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>		
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>		
Date of submission of the demand  <b>08.06.2005</b>	Date of completion of this report  <b>23.11.2005</b>	
Name and mailing address of the International preliminary examining authority:   <b>European Patent Office</b> <b>D-80298 Munich</b> <b>Tel. +49 89 2399 - 0 Tx: 523656 epmu d</b> <b>Fax: +49 89 2399 - 4465</b>	Authorized Officer  <b>Baston, E</b>  Telephone No. +49 89 2399-8229  	

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/IB2004/002527

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**Box No. I Basis of the report**

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1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
  - ☐ publication of the international application (under Rule 12.4)
  - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements\*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

**Description, Pages**

2-17	as originally filed
1	received on 08.06.2005 with letter of 07.06.2005

**Claims, Numbers**

1(part), 2-13	as originally filed
1(part)	received on 08.06.2005 with letter of 07.06.2005

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/IB2004/002527

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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**1. Statement**

Novelty (N)	Yes: Claims	1-13
	No: Claims	
Inventive step (IS)	Yes: Claims	1-13
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-13
	No: Claims	

**2. Citations and explanations (Rule 70.7):**

**see separate sheet**

**To section V**

The following documents were cited in the search report and were considered for the examination of the present application:

- D1: EP-A-0 240 228 (ICI AMERICAS INC) 7 October 1987
- D2: WO 01/55125 A (EGIS GYOGYSZERGYAR RT; BOZSING, DANIEL; KOVANYINE LAX, GYOERGYI; SIMIG) 2 August 2001
- D3: EP-A-0 282 236 (IMPERIAL CHEMICAL INDUSTRIES PLC) 14 September 1988
- D4: WARAWA E J ET AL: "Behavioral approach to nondyskinetic dopamine antagonists: Identification of Seroquel" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 44, 1 February 2001 (2001-02-01), pages 372-389,
- D5: LAMBERT, T.N. ET AL.: "Synthesis of 3-Hydroxy-2-pyridinone Derivatives of 4-tert-Butylcalix[4]arenes: A New Class of Selective Extractants of Actinide(IV) Ions" JOURNAL OF ORGANIC CHEMISTRY, vol. 64, 1999, pages 6097-6101.

The present application is directed to a process for the preparation of 11-(4-[2-(2-HYDROXYETHOXY)ETHYL] -1-PIPERAZINYL)-DIBENZO[B,F][1,4]THIAZEPINE, a compound which is known for its neuroleptic or antipsychotic activity. The process consists in the reaction of an intermediate alcohol (II) with an alkylating agent which has a protected alcohol function. The target compound is obtained by a deprotection step.

The documents of the prior art anticipate processes where the side chain is introduced by reaction of e.g. 2-chloroethoxyethanol with a piperazine precursor (D1) or by reaction of ethylene glycol with a halo derivative (D2). The process anticipated in document D5 makes also use of an alkylating agent similar to formula (III), but for the preparation of a different target compound.

The description contains sufficient data which reveal that the process is suitable to obtain the target compound in high yield and good purity.

The requirements of Art. 33(2)(3) PCT are met.

**INTERNATIONAL PRELIMINARY  
REPORT ON PATENTABILITY  
(SEPARATE SHEET)**

International application No.

PCT/IB2004/002527

1

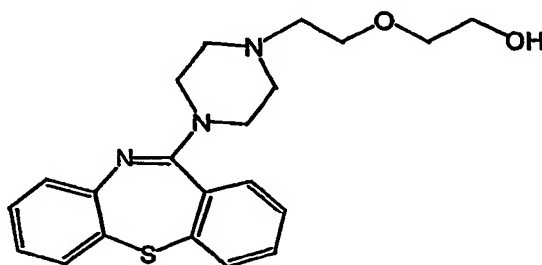
**PROCEDURE FOR PREPARING 11-(4-[2-(2-HYDROXYETHOXY)ETHYL]-1-PIPERAZINEYL)-DIBENZO[B,F][1,4]THIAZEPINE**

**5 Field of the invention**

This invention relates to a new procedure for the preparation of a pharmaceutically active compound.

**Background of the invention**

10 Patent EP 240228 describes a dibenzothiazepine compound of formula (I):



(I)

15

useful for its antidopaminergic activity, for example as an antipsychotic or neuroleptic, currently known by the DCI of quetiapine.

20 The said patent describes the obtaining of the compound of formula (I) by reaction of an imino chloride, specifically 11-chloro-dibenzo[b,f][1,4]thiazepine, or of its corresponding imino ether, with 2-(2-piperazine-1-yl-ethoxy) ethanol.

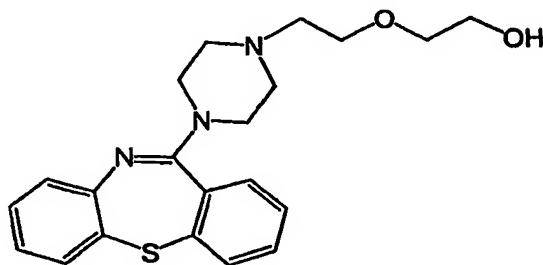
25

A later patent, EP 282236, describes the preparation of the compound of formula (I) by reaction of the same imino chloride with piperazine, followed by reaction of the product obtained in hydrochlorate form with chloro-30 ethoxyethanol.

18

**CLAIMS**

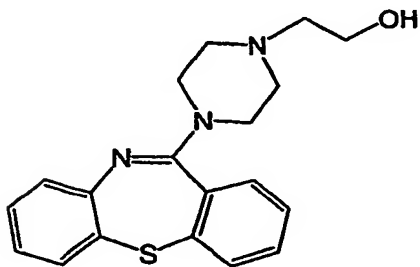
1. Procedure for obtaining 11-(4-[2-(2-  
5 hydroxyethoxy)ethyl]-1-piperazinyl)-  
dibenzo[b,f][1,4]thiazepine, of formula (I)



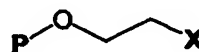
10

(I)

or a pharmaceutically acceptable salt thereof,  
characterised in that it comprises reaction between a  
15 compound of formula (II) and a compound of formula (III):



(II)



(III)

20

in which X means a leaving group and P a protective group  
of alcohols resistant to alkaline conditions, in the  
presence of a base, followed by a step of deprotection